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EXAMINER	
BRISTOL, LYNN ANNE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,409	LEDBETTER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *414-445* is/are pending in the application.

4a) Of the above claim(s) *417,419,421,427,432-434 and 440-445* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *414-416,418,420,422-426,428-431, 437 and 439* is/are rejected.

7)☒ Claim(s) *435, 436 and 438* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/08, 1/14/09, 5/5/09 and 5/26/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 414-445 are all the pending claims for this application.

2. Applicants have withdrawn Claims 417, 419, 421, 427, 432-434 and 440-445 in the Response of 3/20/09.

3. The Office Action of 2/20/09 indicates under sections 10-12 that election of additional species would require additional fees. The examiner respectfully apologizes for the error in having used the improper form paragraphs under MPEP 1800. Accordingly, this being a 371 National Stage application, the proper form paragraph should have been “18-20” and not “18-17” thru “18-19.”

4. The amendments to the specification 11/25/08, 2/26/09 and 3/20/09 have been considered and entered.

Election/Restrictions

5. Applicant's election with traverse of Group I (Claims 414-439) in the reply filed on 3/20/09 is acknowledged. The traversal is on the ground(s) that:

“(US 2005/0084933, "Schilling" and US 6,623,940, "Ledbetter"), either alone or in combination, fail to teach or suggest the fusion protein of claim 414. More specifically, neither of these references discloses a proline mutation in the hinge polypeptide as recited in subpart (ii) of claim 414. For example, Schilling relates to methods for increasing protein sialylation by feeding cultured cells with D-galactose. The only disclosure relevant to the fusion protein of the present application is CTLA4Ig as shown in Figure 8. In the sequence shown in Figure 8, a serine is at position +148 instead of a proline in the wild type human IgG1 CH2 domain. Position +148 in Figure 8 of Schilling corresponds to position 238 of the present application, which is described throughout the present application as in a CH2 domain (see, e.g., the third to the last paragraph describing Figure 69 on

page 96, the sentence bridging pages 205 and 206, the first sentence in Example 28 on page 226, the last sentence of Example 43 on page 244, and brief description of SEQ ID NOS:91 and 92 on page 337 of the substitute specification filed February 26, 2009), not in a hinge region as asserted in the Restriction Requirement. Similarly, the proline to serine substitution in the sequences of Ledbetter is at the same position as position +148 in Schilling and also corresponds to position 238 of the present application. As indicated on page 4 of the Restriction Requirement and also shown in Figure 4A of Ledbetter, this position is in the CH2 domain, not in the hinge region.

This is not found persuasive with respect to Schilling (US 2005/0084933) in view of Ledbetter because Schilling teaches in general making a fusion protein recognizing CD antigens, and provides an example of a fusion protein using CTLA-Ig, where within an altered hinge region of the molecule there is a proline to serine mutation. Schilling teaches: "For example, mutations in the Ig moiety can include changes in any or all of its cysteine residues within the hinge domain. For example, as shown in FIG. 8, the cysteines at positions +130, +136, and +139 are substituted with serine. The Ig moiety can also include the proline at position +148 substituted with a serine, as shown in FIG. 8" [0212].

Applicants have not shown by sequence alignment how position +148 of Schilling corresponds to the CH2 domain of the instant application. None of the inventors are the same and thus it is unclear what overlap exists between the sequences per se between the reference and the instant claims. Ledbetter (US 6,623,940) teaches making CD20 binding fusion proteins with altered hinges.

Still further, Applicants generic claims broadly read on any anti-CD20 fusion protein comprising "(ii) an ***altered*** wild type immunoglobulin hinge polypeptide, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated." What does altered mean? The wild-type hinge can be altered

in any unlimited way including the length and the amino acid composition, and mutating a proline to a serine within the altered hinge region is encompassed by the limitation. Still further, element (iii) recites "an amino-terminally truncated immunoglobulin heavy chain constant region polypeptide" which is undefined by the claims. Thus as discussed below, the region of the fusion protein corresponding to the overlap between elements (ii) and (iii) is not well described in the instant claims, and therefore the cited references are considered to break unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 440-445 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/20/09.

Claims 417, 419, 421, 427, 432-434 are withdrawn pursuant to Applicants pending claim sheet.

7. Applicant's election of species for "(b) the second cysteine is substituted with serine" (Claim 431) and "SEQ ID NO: 246 (2H7 scFv VHLIIS (CSC-S)H WCH2 WCH3)" (Claim 435) in the reply filed on 3/20/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The non-elected species of hinge (Claim 431) are withdrawn from examination.

The non-elected species of fusion protein in Claim 435 have been *rejoined* for examination.

8. Claims 414-416, 418, 420, 422-426, 428-431, and 435-439 are all the pending claims under examination.

Priority

9. Applicants priority claim was discussed in the Office Action of 2/20/09. Applicants have not addressed the examiner's comments, and the priority filing date for the instant claims is 12/24/03.

Information Disclosure Statement

10. The IDS' of 1/11/08, 1/14/09, 5/5/09 and 5/26/09 have been considered and entered. The initialed and signed copies of the 1449 forms are attached.

11. If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

12. Claims 414-416, 418, 420, 422-426, 428-431, 437 and 439 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are interpreted as being drawn to a CD20-binding fusion protein comprising in element "(ii) an altered wild type immunoglobulin hinge polypeptide, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated." The genus of hinge polypeptides is not nearly supported by the specification and prior art. Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials 3/29/08), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The specification discusses the classes of hinges for the antibody isotypes at [0042-0043] and the core hinge region of human IgG1 contains the sequence Cys-Pro-Pro-Cys which, when dimerized by disulfide bond formation, results in a cyclic octapeptide believed to act as a pivot, thus conferring flexibility [0043]. The specification teaches a "connecting region" or what appears to be the same as a hinge where all of the cysteines and one proline have been changed to serines (SSS-S). The specification does not teach the extent to which the wild type hinge region can be altered much less the extent of amino acid modification or those amino acids that are permissible for substitution for the proline to the extent the hinge would still be functional to act as a flexible pivot.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the genus of "altered wild type hinge region, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated" and where the resultant fusion protein is still flexible.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of "altered wild type hinge region, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated" and where the resultant fusion protein is still flexible.

d) Method of making the claimed invention: the specification teaches

examples of antibody hinge regions and the methods for mutagenizing the hinge residues.

e) Level of skill and knowledge in the art: the cloning of antibody hinge regions and generating modifications in the hinge for identifying functional regions was well established at the time of the invention.

f) Predictability in the Art: the art does not appear to teach where within any wild-type hinge polypeptide, any alteration can be introduced, for example to the length and or composition, where the resultant CD20-binding fusion protein is still flexible and maintains antigen specificity. In general the art recognizes the importance of the Ig hinge where according to Dorrington et al. (Arch. Immunol. Ther. Exp. 29(3): 275-282 (1981); Abstract only) teach the importance of length and disulfide bonds in the hinge for conferring flexibility and variation in the distance between the hypervariable regions.

Applicants have not demonstrated with sufficient evidence the genus of "altered wild type hinge region, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated" and where the resultant fusion protein is still flexible. The ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of fusion proteins at the time of application filing.

Enablement

13. Claims 414-416, 418, 420, 422-426, 428-431, 437 and 439 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being

enabling for a fusion protein having binding specificity for CD20 comprising complementary VH and VL domains and complementary VH CDR 1-3 and VL CDR 1-3 domains and the fusion proteins of Claims 435, 436 and 438,

does not reasonably provide enablement for fusion proteins comprising for element (i) of Claim 414: a single variable domain, or variable domains comprising any substitution at any one or more positions 9, 10, 11, 12, 108, 110 or 112 in the VH domain; and for element (ii) of Claim 414 any altered wild type hinge; and for any fusion protein having 99% identity to the fusion protein of SEQ ID NO:166 or 246 (Claim 437). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to:

> "414. (Previously Presented) A fusion protein comprising from amino- terminus to carboxy-terminus: (i) an immunoglobulin binding domain polypeptide that binds CD20; (ii) an altered wild type immunoglobulin hinge polypeptide, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated; and (iii) an amino-terminally truncated immunoglobulin heavy chain constant region polypeptide."

The relative skill in the art required to practice the invention is a molecule immunologist.

Disclosure in the Specification

The specification shows working examples for the species:

SEQ ID NO:135 (2H7 scFv (CSS-S)H WCH2 WCH3), wherein proline at position 283 is substituted with serine,

SEQ ID NO:137 (2H7 scFv (SCS-S)H WCH2 WCH3), wherein proline at position 283 is substituted with serine,

SEQ ID NO:166 (2H7 scFv (CSC-S)H WCH2 WCH3), wherein proline at position 283 is substituted with serine,

SEQ ID NO:372 (2H7 scFv VHL11S (CSS-S)H WCH2 WCH3),

SEQ ID NO:246 (2H7 scFv VH L11S (CSC-S)H WCH2 WCH3),

SEQ ID NO:370 (2H7 scFv VH L11S (SSS-S)H WCH2 WCH3),

SEQ ID NO:268 (2H7 scFv VH L11S (CSS-S)H K322S CH2 WCH3),

SEQ ID NO:276 (2H7 scFv VH L11S (CSS-S)H P331S CH2 WCH3) *and*

a CD20 binding fusion protein comprising from amino-terminus to carboxy-terminus: (i) an scFv binding domain polypeptide that binds CD20, wherein the scFv comprises an immunoglobulin light chain variable region polypeptide consisting of amino acids 23-128 as set forth in SEQ ID NO:689, a linker peptide consisting of amino acids 129-144 as set forth in SEQ ID NO:246, and an immunoglobulin heavy chain variable region polypeptide consisting of amino acids 145-265 as set forth in SEQ ID NO:689, wherein leucine 155 of the heavy chain variable region polypeptide is substituted with serine, (ii) an immunoglobulin hinge polypeptide consisting of amino acids 267-283 as set forth in SEQ ID NO:246; and (iii) an amino-terminally truncated immunoglobulin heavy chain constant region polypeptide consisting of amino acids 284-500 as set forth in SEQ ID NO:246.

The specification is not enabling for producing a CD20 binding domain-immunoglobulin fusion protein where the binding domain polypeptide comprises

the myriad possible VH or VL regions or the myriad possible hinge mutations that would allow proper folding of the fusion protein much less that any properly folded fusion protein could even maintain its CD20 binding activity because of the myriad possible variable domain regions.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed fusion protein in a manner reasonably correlated with the scope of the claims broadly including single variable domain binding regions, amino acid substituted VH domains, and fusion proteins having any altered hinge region, or fusion proteins having at least 99% identity to the fusion proteins of SEQ ID NOS: 166 or 246 without teaching a structure/function correlation for the myriad species of fusion protein. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: Modified CDRs affect antigen specificity

The claims encompass CD20 binding fusion proteins comprising a single variable domain and less than the full complement of VH/VL CDRs. The claims encompass modifications as amino acid substitutions to the VH domain. The claims encompass fusion proteins having at least 99% identity to the fusion

proteins of SEQ ID NOS: 166 or 246 without identifying the structural differences and where they occur between in the species. Applicants have not shown that any fusion protein comprising less than a full complement of VH/VL CDRs from a parent CD20 antibody would retain the antigen binding for CD20. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework regions influence binding.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

De Pascalis *et al.* The Journal of Immunology (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (2003) BBRC 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide

was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (2002) J. Mol. Biol. 320, 415-428 additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (2007) Mol. Immunol. 44: 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* J. Mol. Bio. (1999) 293, 865-881 describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* J. Mol. Biol. (1999) 294, 151-162 state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that

accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single variable domain makes a significant contribution in the antigen binding, the residues in these domains are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single variable domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single variable domain (or less than full complement of VH and VL CDRs).

Analyzing applicants own disclosure, which while it does have divergent CDR residues, the majority of these heavy chain CDRs were paired with specific light chain CDRs. Additionally, the data seem to indicate that it is the frameworks and variable domain enabled for CD20 antigen binding.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass fusion proteins comprising VH domains comprising amino acid substitutions. It is not well established in the art that all variable domains are amenable to substitutions much less conservative modifications. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al*. (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody

(Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al*., Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects, and these three references demonstrate the unpredictability in the art as far as demonstrating that any conservative substitution within any CDR can be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, “a very conservative substitution may abolish binding” while “in another, a non-conservative substitution may have very little effect on the binding” (p. 35, Col. 1, ¶1).

Dufner (Trends Biotechnol. 24(11):523-29 (2006)) teaches: “specific structural information - on the antibody to be optimized, its antigen and their interaction- is rarely available or lacks the high resolution required to determine accurately important details such as side-chain conformations, hydrogen-bonding patterns and the position of water molecules” (p. 527, Col. 2, ¶1). Applicants

specification and the evidence of record does not define specific structural information detailing the number of and exact position of hotspots in the CDRs which “can vary considerably from case to case and therefore cannot be predicted" (legend to Figure 2 of Dufner). Thus even with the availability of screening approaches as taught in the specification and Dufner, the ordinary artisan could not predict the hotspots much less those residues critical for conferring specific antigen binding for any of the claimed CDRs and variable domains absent further additional information and experimentation. What does a sequence alignment for the variable domains, CDR regions or frameworks regions look like for a "reasonable" number of CD20 fusion proteins having least 99% identity with the VH and VL domain of the fusion proteins of SEQ ID NOS: 166 or 246 that would guide the ordinary artisan in determining the important common shared or similar binding residues that confer specific antigen binding? Are any hotspots present in the CDRs (or FRs), what is the frequency of those hot spots and what are the positions of those hot spots?

Prior Art Status for Single Variable Domain Antibodies

The claims encompass CD20 binding fusion proteins comprising a single variable domain and less than the full complement of VH/VL CDRs.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/ Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of fusion proteins as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Furthermore, while the level of skill required to generate the fusion proteins is that of a molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified

antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody), and then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted polypeptide or antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

> said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 414, 415, 420, 422, 423, and 425-429 are rejected under 35 U.S.C. 103(a) as being obvious over Schilling (US 20050084933; published April 21, 2005; filed December 18, 2003; cited in the PTO 892 form of 2/20/09) in view of Ledbetter et al. (USPN 6623940; published September 23, 2003; cited in the PTO 892 form of 2/20/09).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are

currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 414, 415, 420, 422, 423, and 425-429 are interpreted as being drawn to a fusion protein comprising from amino- terminus to carboxy-terminus: (i) an immunoglobulin binding domain polypeptide that binds CD20; (ii) an altered wild type immunoglobulin hinge polypeptide, wherein a proline in the wild type immunoglobulin hinge polypeptide has been mutated; and (iii) an amino-terminally truncated immunoglobulin heavy chain constant region polypeptide (Claim 414), the binding domain comprises a HL and VH domain (Claim 415), the binding domain is a scfv (Claim 416), the fusion protein binds CD20 on a tumor cell (Claim 422), the fusion protein comprising a VL and VH domain linked by a Gly-Gly-Gly-Ser linker (Claim 423), the fusion protein comprising a CH2 domain attached to a CH3 domain (Claim 425), and the CH2 and CH3 domains are an IgA, IgD, or IgG constant region peptides (Claim 426), the constant region comprises an IgE CH3 constant region polypeptide attached to an IgE CH4 constant region polypeptide (Claim 427), the hinge is from IgG, IgA or IgE (Claim 428) and the hinge is an altered human IgG1, IgG2, IgG3, or IgG4 hinge region (Claim 429).

The fusion protein was prima facie obvious at the time of the invention over Schilling and Ledbetter.

Schilling teaches generating fusion proteins [0157], using the CTLA4Ig protein as a working embodiment comprising the extracellular domain of CTLA4 joined to an Ig moiety comprising all or a portion of an immunoglobulin molecule, or a portion of an immunoglobulin constant region such as all or a portion of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD or IgE which include the hinge, CH2 and CH3, and mutated forms of the constant region [0195; 0212]. Schilling teaches:

"The Ig moiety can have one or more mutations therein, (e.g., in the CH2 domain to reduce effector functions such as CDC or ADCC) where the mutation modulates the capability of the Ig to bind its ligand by increasing or decreasing the capability of the Ig to bind to Fc receptors. For example, mutations in the Ig moiety can include changes in any or all of its cysteine residues within the hinge domain. For example, as shown in FIG. 8, the cysteines at positions +130, +136, and +139 are substituted with serine. The Ig moiety can also include the proline at position +148 substituted with a serine, as shown in FIG. 8" [0212].

The elements (ii) and (iii) for Claim 414 are drawn to any altered hinge which is limitless in size and composition and requires a substituted praline in addition to hinge being linked to any amino-terminally truncated heavy chain constant region, thus absent any description of this overlapping region of the fusion protein, it is the examiner position that Schilling reads on a fusion protein with an altered hinge and having the proline substitution.

The difference between the prior art of Schilling and the claimed fusion protein is that the fusion protein of Schilling does not expressly include an scfv as the binding domain and having the linker sequence of Gly-Gly-Gly-Ser and binding CD20 on a tumor cells.

Ledbetter teaches fusion proteins comprising a scfv having a linker comprising Gly-Gly-Gly-Gly-Ser and binding CD20 on tumor cells. The instant claims recite that the linker comprises Gly-Gly-Gly-Ser would be inclusive of the linker Gly-Gly-Gly-Gly-Ser.

At the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Schilling and Ledbetter to use the fusion protein of Schilling comprising any altered hinge domain and comprising a substituted proline falling within the transition region between the altered hinge and the truncated constant region of the fusion protein for producing the CD20-binding fusion protein of Ledbetter where the heavy and light chain variable domains were present in the construct with the linker sequence and the fusion protein having the ability to bind CD20 on tumors. One would have been motivated to do this because of the advantages of producing a fusion protein according to Inouye, and the advantages of including both the heavy and light chain variable domains in a scfv as noted by Ledbetter. One would have had a reasonable expectation of success to modify the fusion protein of Schilling to increase the repertoire of fusion proteins according to Ledbetter to produce a CD20 binding fusion protein because of the results of Schilling and Ledbetter. Therefore, the fusion protein of claims 414, 415, 420, 422, 423, and 425-429 would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

15. No claims are allowed.

16. Claims 435, 436 and 438 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority